

Reviews

Progress in Study on Synergism and Detoxification of Chinese Medicine for Glucocorticoid

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Abstracts: Glucocorticoid (GC) plays an important role in anti-inflammatory, anti-allergic effects and immunosuppression, and has become a widely used drug in clinical departments. However, GC also produces a number of serious side effects at the same time. After GC acting on human body, the syndrome change has some regular pattern and it can be treated on the basis of syndrome differentiation and stage to aim at further improving therapeutic efficacy. The Chinese medicine can reduce the side effects of GC when treating the primary disease, thus plays a role in Synergism and Detoxification.

Keywords: *Glucocorticoids; Chinese medicine; synergism; detoxification; review*

Glucocorticoid (GC) plays an important role in anti-inflammatory, anti-allergic effects and immunosuppression, and can control a number of critical or intractable illness seizures. However, it often causes long-term dependence in treating chronic diseases, especially vulnerable to those who take it for a long time orally in which hypothalamic-pituitary-adrenal-thymus (HPAT) axis is inhibited, and then the reserve capacity of pituitary and adrenal cortex declines. A sudden stop or rapid decrement of GC will result in disease recurrence, even a crisis. Certain regularity could be found in terms of clinical manifestations, symptoms and signs of patients treated with GC. Therefore, to study the law of GC effect on changes of human body and choose the corresponding Chinese medicine in treatment will not only enhance the effectiveness of treatment, but also reduce the incidence of GC adverse reactions.

Understanding of GC in Traditional Chinese Medicine

1. The nature, flavor and attributive channel of GC

It is explained in TCM that the nature of GC pertains to pure yang.¹ Under physiological conditions, stress state, and in small dosage substitution therapy, it is a medicine of pure yang. However, its pharmacologic and adverse actions, such as anti-inflammatory, immune suppression, negative nitrogen balance, etc. pertain to yin. So according to the principle to decide the nature of a medicine, it is cold in property, bitter in flavor and acts on the kidney meridian.² It is also held that GC has physiological effects of physical fire (少火) and side effects of evil fire (壮火).

2. The efficacy and indications of GC³

Reinforcing fire and strengthening yang, warming and nourishing spleen and kidney: for adrenocortical hypofunction. Elevating kidney yang, reviving yang for resuscitation: for collapse of yin and yang, or depletion

of *qi* syndrome. Mobilizing kidney yin and water to fight fire: for the syndrome of Yingfen (nutrient system 营分), Xuefen (blood system 血分) and pericardium invaded by heat-toxicity. Warming the spleen to resolve dampness: for edema caused by yang deficiency of the spleen and kidney. Dispelling wind and relieving itching: for eczema, asthma, purpura, etc. caused by pathogenic wind. Regulating *qi*-blood and yin-yang: for fever, limb pain, myasthenia, etc. caused by pathogenic wind, damp and heat, *qi*-blood and yin-yang imbalance.

The Influence of GC on Syndrome

Syndrome is a reflection of the nature of a disease in a certain stage, which reflects the pathogenic factors and the state of the body response to them, and summarizes the pathology essence in the current stage of a disease, including the location, pathogenic factors, nature, and development of a disease, etc.⁴ Therefore, the influence of GC on syndrome is a reflection of the nature of both therapeutic and side effects on human body.

Luo, et al.⁵ observed and analyzed the changes of TCM symptoms and signs and TCM differential types of 220 adult patients with idiopathic nephrotic syndrome treated with prednisone. The prednisone application was in three levels, large, small and maintaining dosage. In studying the primary symptoms, it was found that 12% of the patients were of yin deficiency type, 58% of yang deficiency, and the remaining 30% of yin-yang deficiency. However, when different dosages were used, these figures changed to 73%, 9%, and 19% respectively

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Supported by Projects in the National Science & Technology Pillar Program in the Eleventh Five-year Plan Period (No. 2006BA104A10), State Traditional Chinese Medicine Department Research Foundation (No. 200707016), National Natural Science Foundation of China (No. 81072764).

with large dosage of prednisone, and to 50%, 10%, and 40% respectively after they took small dosage of prednisone, and to 16%, 26%, and 46% after taking a maintaining dosage. Meanwhile, in studying the incidental symptoms, it was found that the patients with toxic heat and damp heat went up obviously from 15% to 61% and 13% to 49% respectively after they took a large dosage, then to 35% and to 45% after taking small dosage. During the entire course of prednisone treatment, changes in patients of accumulated fluid damp type reduced evidently compared to that of blood stasis and *qi*-stagnation types. These changes are closely related to the dosage of prednisone. So, a correct syndrome differentiation is helpful to improve the therapeutic effect of prednisone and can reduce adverse reactions.

Wang, et al.⁶ indicated that in the prednisone application process, regardless of external symptoms and signs, the inherent essence at early stage is yin deficiency caused by internal heat according to experimental observation. Symptoms of adrenocortical hyperfunction in the stage of high-dose prednisone were differentiated as hyperactivity of fire due to yin deficiency syndrome based on syndrome differentiation, while in prednisone withdrawal or stopping stage, symptoms of adrenal dysfunction were differentiated as a kidney-yang deficiency syndrome. Many scholars believed that the long-term or large-scale use of prednisone could cause blood stasis, kidney deficiency and consumption of anti-pathogenic *qi*.

Synergism of TCM to GC

1. High dose GC period

Ren, et al.⁷ treated 36 children with henoch-schonlein purpura nephritis by randomly assigning them to two groups, the control group (18 cases) was treated with GC, the treated group (18 cases), besides the GC treatment, Zidian Shenning Decoction (紫癜肾宁方) was given additionally. GC was taken orally in 1.0–1.5 mg/kg per day for 8 weeks. Zidian Shenning Decoction mainly consists of Shui Niu Jiao (Cornu Bubali), Sheng Di (Radix Rehmanniae), Chi Shao (Radix Paeoniae Rubra), Dan Pi (Cortex Moutan), Huang Qi (Radix Astragali), Zi Cao (Radix Arnebiae), Yi Mu Cao (Herba Leonuri), Chan Tui (Periostracum Cicadae), Nü Zhen Zi (Fructus Ligustri Lucidi), etc. After 8 weeks treatment, 24 h urine protein and 12 h urine red blood cell count of both groups decreased significantly compared with pre-treatment ($P<0.05$), and the treated group did more significantly compared with the control group ($P<0.05$). Danshen Zhushuye (丹参注射液 Salviae Miltiorrhizae Injection)⁸ and high-dose methylprednisolone were used in the treatment of nephritic syndrome. Thirty patients in the combined treatment group received Salviae Miltiorrhizae Injection and high-dose methylprednisolone, serum creatinine and urea nitrogen markedly decreased ($P<0.05$), but serum albumin increased significantly ($P<0.05$), compared with

high-dose methylprednisolone randomly control group (30 cases). Gu, et al.⁹ used Zishenqing Decoction (自身清), consisting of Sheng Di (Radix Rehmanniae), Huang Qi (Radix Astragali), Bai Zhu (Rhizoma Atractylodis Macrocephalae), Gan Cao (Radix Et Rhizoma Glycyrrhizae), Bai Hua She She Cao (Herba Hedyotidis Diffusae), Dan Pi (Cortex Moutan), Chong Lou (Rhizoma Parudis), etc., to intervene 30 patients with active erythematosus (SLE). The other 30 patients were randomly assigned to the control group in the treatment of GC only. The dosage of GC in the treatment group kept decreasing and was significantly lower than that in the control group, moreover, the proportion of yin deficiency type and toxic heat type markedly reduced.

Therefore, using heat-clearing, blood-cooling and yin nourishing Chinese medicine in high dose GC period can alleviate the symptoms, improve the therapeutic effect, and create conditions for further reduction of the GC dosage of later period.

2. GC withdrawal period

Fan, et al.¹⁰ made a randomized controlled trial on 147 patients with systemic lupus SLE. The control group (68 cases) was treated mainly with prednisone only, while the integrated traditional Chinese and western medicine (ITCWM) group (79 cases) with Jiedu Quyu Ziyin (the method of removing toxic factors and blood stasis, and nourishing yin 解毒祛瘀滋阴法) on the basis of prednisone. Both groups were treated for 2 courses, 3 months as a therapy course. After 6 months, the trial showed that the prednisone dosage of the ITCWM group was lower than that in the control group with significant difference ($P<0.05$), and the total prednisone dosage in the ITCWM group was markedly lower than that in the control group ($P<0.01$). The ratio of cases who had to add prednisone for aggravation of disease in the ITCWM group (5.06%) was less than that in the control group (13.24%) significantly ($P<0.05$). The levels of adreno-cortico-tropic-hormone (ACTH) and Cortisol (CS) in the ITCWM group were significantly better than those in the control group ($P<0.05$). Similar results were obtained by Jin, et al.,¹¹ who used Ziyin Langchuang Jiaonang (滋阴狼疮胶囊 Capsule for Systemic Lupus Erythematosus by Nourishing Yin) to treat SLE in GC withdrawal period.

Liu, et al.¹² classified 24 patients with SLE into four syndrome types, i.e. the excessive noxious heat-*qi* and blood vigorous heat type, the *qi* and yin deficiency-obstruction of blood circulation type, the deficiency of spleen and kidney-stagnation of *qi* and blood stasis type, and the spleen deficiency and liver stagnation-blockage of channel type. He treated patients respectively with his self-formulated decoction by syndrome differentiation. Compared with the randomly controlled group (23 cases) which get the treatment of GC only, the general efficacy of the treated group was significantly better ($P<0.05$),

and the prednisone dosage of it decreased markedly ($P<0.01$).

In GC withdrawal period, Chinese medicine can speed up GC withdrawal, and reduce the maintenance dose and the total dose, to reduce the side effects caused by GC.

3. GC maintaining dosage period

Guo, et al.¹³ used the empirical TCM recipe Yiqi Yangyin Decoction (益气养阴汤 Supplement *Qi* and Nourish Yin), consisting of Mai Dong (Radix Ophiopogonis), Wu Wei Zi (Fructus Schisandrae Chinensis), Tai Zi Shen (Radix Pseudostellariae), Huang Qi (Radix Astragali), Dang Gui (Radix Angelicae Sinensis), Shan Yu Rou (Fructus Corni), Huai Shan Yao (Rhizoma Dioscoreae), Huang Jing (Rhizoma Polygonatum), Shu Di Huang (Prepared Radix Rehmanniae), Qin Jiao (Radix Gentianae Macrophyllae), Ban Zhi Lian (Herba Scutellariae Barbatae), etc., to treat 30 patients with SLE in remission stage. They also enrolled 10 patients treated by simple western medicine as control. The result showed that the Decoction could increase the total effective rate considerably, and decrease the maintaining dose of prednisone significantly, in comparison with the control group ($P<0.05$). Moreover, the immune parameters (IgG and C3) were significantly improved after treatment in the treatment group ($P<0.01$).

Wenshen No. I (温肾 I 号 Kidney Warming No.I) was used to treat steroid-dependent refractory nephrotic syndrome. It mainly consists of Huang Qi (Radix Astragali), Xian Ling Pi (Herba Epimedii), Lu Jiao Jiao (Colla Cornus Cervi), Zi He Che Fen (Placenta Hominis Power), Tu Si Zi (Semen Cuscutae), Dang Gui (Radix Angelicae Sinensis), Dan Shen (Radix Salviae Miltiorrhizae), Di Long (Lumbricus), etc. The clinical study by Pan, et al.¹⁴ illustrated that combination of Wenshen No. I and Western medicine could be more effective in lowering 24 h urine protein, serum creatinine and urea nitrogen ($P<0.05$), and increasing serum total protein and albumin ($P<0.05$) than in the randomly control western medicine group. Yi, et al.¹⁵ also acquired similar effect in treating refractory nephrotic syndrome with Huoba Huagen Pian (火把花根片 Colquhounia Root Tablet).

In GC maintaining dosage period, Chinese medicine can improve biochemistry index and then further increase therapeutic effect.

4. Others

Kou, et al.¹⁶ did Meta-analysis on efficacy of tripterygium glycosides (TG) and GC for nephritic syndrome. The results showed that TG combined with GC had good effects in reducing the recurrence. Clinical observation on 60 SLE patients carried out by Yang, et al.,¹⁷ 118 patients by Chen, et al.¹⁸ and 52 patients by Zhang, et al.¹⁹ all showed that the improvement rate in

yin deficiency and fire excess syndrome marked by the symptoms of hair loss, hypodynamia, vexation, nausea and vomiting, edema, abnormal menstruation, and the complaints of dental ulcer, lassitude, insomnia, was higher than that in the control group or before the Chinese medicine treatment respectively ($P<0.05$ or $P<0.01$).

Wen, et al.²⁰ did researches on the quality of life (QOF) of the patients with SLE by short form-36 (SF-36), before and after they were treated by TCM Jiedu Quyu Ziyin method. The control group (68 cases) was treated mainly with prednisone only, while the ITCWM group (79 cases) with TCM Jiedu Quyu Ziyin method on the basis of prednisone. After 6-month treatment, the ITCWM group had better effect than the control group on the QOF.

Detoxification of TCM to GC

1. Effects on bone metabolism

Chen, et al.²¹ used Bugu Capsule (补骨胶囊 Capsule for Strengthening the Bone) consisting of Yin Yang Huo (Herba Epimedii), Huang Qi (Radix Astragali), Bai Zhu (Rhizoma Atractylodis Macrocephalae), etc. to treat 34 patients with SLE in the treatment of GC, and also enrolled 32 patients as the control. The course of treatment was 6–18 months. The incidence of osteoporosis or osteopenia in treated group (2 cases) was decreased significantly ($P<0.05$), compared with the control group (9 cases). Fan, et al.²² controlled GC-induced osteoporosis in SLE with Jiedu Quyu Ziyin methods. The control group (68 cases) treated mainly with prednisone only, while the ITCWM group (79 cases) with Jiedu Quyu Ziyin method on the basis of prednisone. Both groups were treated for 6 months. The levels of serum P, 25-(OH) D₃, alkaline phosphatase (ALP), serum bone gla protein (BGP) and bone mineral density (BMD) in the ITCWM group were significantly higher than those in the control group ($P<0.05$), and the lever of urinary calcium and parathyroid hormone (PTH) were also lower obviously ($P<0.05$).

2. Effects on lipid metabolism and hemorheology

Xuezhikang (血脂康 Capsule for Lipid),²³ a Chinese medicine preparation made from extract of a specially made Red Koji (红曲) after the fermentation with its active ingredient lovastatin and a variety of lipid-lowering composition, can generally adjust the lipid spectrum, and may exist beyond the protective effect of lipid. Yang, et al.²⁴ used Xuezhikang capsule to treat the patients of nephrotic syndrome with hyperlipidemia, who were randomly divided into Xuezhikang group (19 cases) and simvastatin group (18 cases). The level of TC, TG and LDL-C were lower obviously ($P<0.01$), and the level of TP, ALB and HDL-C significantly increased ($P<0.01$ or <0.05) in both groups, and no significant differences were found in both groups before and after the treatment ($P>0.05$). The result of the study conducted by Wang, et

al.²⁵ also concluded that Jiedu Quyu Ziyin methods could prevent and cure corticosteroid hyperlipemia of SLE.

The randomized controlled clinical trial by Wu, et al.²⁶ displayed that the total effective rate (88.7%) of GC and Western medicine supportive treatment combined with Shuizhi Zhushu Injection (水蛭注射液 Injection of Leech) in treating primary nephrotic syndrome was better than that (70.4%) of Western medicine alone ($P<0.05$) with significant difference between the two in aspects of the level of TC and TG, high and low shear rate and blood sedimentation rate ($P<0.05$ or $P<0.01$). The study by Nie, et al.²⁷ showed that Xueshuantong (血栓通 Thrombus Removal) and Dengzhan Xixin Zhushu (灯盏细辛注射液 Injection of Herba Erigerontis) had the lipid-lowering and anticoagulative effects bringing no major adverse events in the treatment of nephrotic syndrome. Pan, et al.²⁸ did researches on the regulation effect of Qize Decoction (芪泽汤 Decoction of Astragalus and Americanwater Plantain) on fibrinogen in the treatment of nephrotic syndrome with GC. Qize decoction consists of Mo Han Lian (Herba Ecliptae), Nü Zhen Zi (Fructus Ligustri Lucidi), Dan Shen (Radix Salviae Miltiorrhizae), Yi Mu Cao (Herba Leonuri), Huang Qi (Radix Astragali), Ze Xie (Rhizoma Alismatis), Shui Zhi (Hirudo), Chuan Xiong (Rhizoma Chuanxiong), etc. The level of fibrinogen in the treated group decreased significantly ($P<0.01$), compared with that of the control group after 2-week treatment.

Wen, et al.²⁹ used the Chinese medicine Lang Chuang Ding (狼疮定 LCD-Systemic Lupus Erythematosus Relieving), consisting of Bai Hua She She Cao (Herba Hedyotidis Diffusae), Chi Shao (Radix Paeoniae Rubra), Sheng Di (Radix Rehmanniae), Shui Niu Jiao (Cornu Bubali), Zi Cao (Radix Arnebiae), Sheng Ma (Rhizoma Cimicifugae), Zhi Bie Jia (Prepared Turtle Shell), on the basis of GC treatment to improve microcirculation of 25 patients with SLE, while the other 20 patients were selected randomly as a control group and treated with GC alone. It showed that the total scores of microcirculation including the shape of loops, blood flow speed, exudates and hemorrhage around the loops in the treated group were better than those of the control group ($P<0.05$) after 3-month treatment, which meant that LCD could effectively alleviate the microcirculation disorders of SLE and improve the therapeutic effect of GC on SLE.

3. Others

Total 100 patients of nephrotic syndrome were treated by Qiu, et al.³⁰ They were randomly divided into two groups, the ITCWM treatment group (treatment group), and the control group. In GC inductive treatment stage, the treatment group was treated with nourishing yin and clearing away heat, cooling and activating blood, and the recipe consisted of Sheng Di (Radix Rehmanniae), Xuan Shen (Radix Scrophulariae), Mai Dong (Radix

Ophiopogonis), Mo Han Lian (Herba Ecliptae), Nü Zhen Zi (Fructus Ligustri Lucidi), Chi Shao (Radix Paeoniae Rubra), Dan Pi (Cortex Moutan), etc, for 8 weeks. In GC decreasing stage, it was treated with tonifying both yin and yang, and the recipe consisted of Huang Qi (Radix Astragali), Tai Zi Shen (Radix Pseudostell), Tu Si Zi (菟 Semen Cuscutae), Bai Zhu (Rhizoma Atractylodis Macrocephalae), Yin Yang Huo (Herba Epimedii), etc, for 6 months. In GC maintaining stage, it was treated with benefiting *qi* to consolidate kidney, strengthening spleen and activating blood, and the basic recipe was composed of Huang Qi (Radix Astragali), Bai Zhu (Rhizoma Atractylodis Macrocephalae), Ba Ji Tian (Radix Morindae Officinalis), Mo Han Lian (Herba Ecliptae), Dang Gui (Radix Angelicae Sinensis), Dan Shen (Radix Salviae Miltiorrhizae), Jin Ying Zi (Fructus Rosae Laevigatae), etc, for 12 months. The rate of adverse reactions such as cushing syndrome, infection, upper gastrointestinal bleeding, hypertension, osteoporosis or femoral head necrosis, etc of the treatment group was significantly lower than that of the control group ($P<0.01$). The study by Zhang, et al.³¹ showed that compared with the simple Western medicinal treatment of SLE, “modified Zibai Dihuang Decoction (加味知柏地黄汤 Modified Decoction of Anemarrhena, Phellodendron and Rehmannia) combined with Western medicine showed significant difference in reducing the occurrence of Cushing’s syndrome.

Tao, et al.³² treated 110 SLE patients who were randomly assigned to 2 groups equally, the control group treated with the conventional Western medicinal treatment and the treated group treated with the same treatment and SLE I formula (in active stage) or SLE II formula (in silent period) respectively. In active stage, it was treated with the method of heat-clearing and detoxifying, and SLE I formula consisted of Sang Bai Pi (Cortex mori), Di Gu Pi (Cortex Lycii Chinensis), Gan Cao (Radix Et Rhizoma Glycyrrhizae), Bai Shao (Radix Paeoniae Alba), Xuan Shen (Radix Scrophulariae), Qing Hao (Artemisia), Zhi Mu (anemarrhena). In silent period, it was treated with the method of nourishing yin and moistening the lung, and SLE II formula consisted of Bai He (Lilium), Tian Dong (Asparagus Root), Mai Dong (Radix Ophiopogonis), Bai Shao (Radix Paeoniae Alba), Dang Gui (Radix Angelicae Sinensis), Xuan Shen (Radix Scrophulariae), Bei Mu (Fritillaria), Jie Geng (Radix Platycodonis), Gan Cao (Radix Et Rhizoma Glycyrrhizae), Dan Zhu Ye (Herba Lophatheri). The incidence of complicated infection and antibiotic utilization rate in the 2-year treatment was 23.6%, 55.0% respectively in the treated group, markedly lower than those (50.9% and 100%) in the control group respectively ($P<0.01$), which meant TCM treatment focusing on the lung could decrease the incidence of complicated infection and the antibiotic utilization rate in SLE patients. It has also been proved by the study by Tao, et al.³³ that besides the above mentioned superiorities, Chinese medicine could regulate T lymphocyte subsets

of the patients with SLE, especially increase CD⁴⁺ T lymphocyte subset, and improve the body's anti-infection ability.

Evaluation and Prospect

Chinese medicines have obtained confirmative efficacies in the treatment of various diseases with GC. Clinical and experimental studies on the synergy and attenuation of Chinese medicine have provided powerful evidences for the clinical application of Chinese medicine. The essence of TCM is "Treatment of diseases based on syndrome differentiation". According to clinical symptoms during GC application, we can treat the primary disease based on syndrome differentiation, and at the same time reduce the side effects of GC, which can complement each other. Now, the researches are mainly focused on the clinical studies of compound Chinese medicine rather than the effective components and mechanism. Therefore, to clarify the efficacy of Chinese medicine, future research should be made to develop the multiple-center, large-sample randomized control trials, and carried out studies on the effective components and mechanism of compound Chinese medicine. In conclusion, Synergism and Detoxification of Chinese Medicine for GC can not only improve the efficacy, but also reduce the side effects of GC, therefore, the study of Chinese medicine is of great significance.

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(Received November 05, 2010)